SYMPTOM MANAGEMENT OVERVIEW

This section provides a quick update of symptomatic conditions in oncology and their management. Readers are invited to submit brief updates following the guidelines at www.JHOPonline.com.

HER2 Receptor Antagonist–Associated Cardiotoxicity

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SYMPTOM OVERVIEW

Human epidermal growth factor receptor 2 (HER2) antagonists have been used in the treatment of breast cancer, with the most well-studied of these agents being trastuzumab. These agents are not, however, wholly benign.1 One class-wide side effect of HER2 antagonists is cardiotoxicity, which manifests most commonly as a dose-independent, reversible cardiomyopathy.2 The incidence of trastuzumab-associated cardiomyopathy varies widely.

Studies in patients with metastatic breast cancer have shown an incidence of cardiac dysfunction of 27% in patients receiving trastuzumab in combination with an anthracycline, and an incidence as low as 3% in patients receiving trastuzumab alone.3 The incidence of cardiomyopathy for the other HER2 antagonists has been reported as 2% for ado-trastuzumab emtansine, 8% to 16% for pertuzumab, and <1% for lapatinib.4-6

The effect of cardiomyopathy on patient morbidity and mortality can be significant. For instance, in the HERA (HERceptin Adjuvant) trial, 0.8% of patients receiving trastuzumab for 1 year and 1.0% of patients receiving trastuzumab for 2 years experienced a primary cardiac end point—defined as severely symptomatic heart failure or cardiac death—compared with 0.1% of patients in the observation arm.7 Therefore, it is imperative that oncology healthcare professionals are able to recognize and manage symptoms of cardiotoxicity from HER2 antagonists. This review will focus primarily on trastuzumab-associated cardiotoxicity, given the wealth of evidence available about this agent compared with other HER2 antagonists. Most trastuzumab-specific information in this review, however, may be extrapolated to other HER2 receptor antagonists.

ETIOLOGY

A variety of risk factors for trastuzumab-associated cardiotoxicity have been identified, the most significant being concomitant use of anthracyclines.8 This risk seems to decline if the administration of trastuzumab sequentially follows an anthracycline, as opposed to being given concurrently. This is safest when the interval between anthracycline and trastuzumab is extended; however, any prior exposure to anthracyclines appears to increase the cardiotoxicity risk. In addition, high cumulative anthracycline doses have been associated with increased risk for trastuzumab-related cardiotoxicity.

Although evidence implicating duration of therapy with increased risk for cardiotoxicity is conflicting, duration of trastuzumab therapy has also been studied as a potential risk factor for trastuzumab-associated cardiotoxicity.8 In addition, older age and specific comorbid conditions (eg, diabetes mellitus, alcohol abuse, kidney dysfunction, use of antihypertensives, and heart disease) have been associated with increased risk. Finally, genetic alterations are being explored as potential risk factors for developing cardiotoxicity. For instance, the HER2 polymorphism Ile655Val has been implicated as a potential risk factor.

The mechanism of HER2 inhibitor–induced cardiotoxicity remains unclear. There is some evidence to suggest that trastuzumab treatment may lead to transient increases in nitrogen-free radical and reactive oxygen species production.9,10 This effect is exacerbated when trastuzumab is used in combination with doxorubicin-induced oxidative and nitrosative stress, which would explain why patients exposed to concomitant anthracyclines are more likely to experience cardiotoxicity than those who are not.10
In addition, blocking of HER2 and cardiomyocytes may eliminate the protective effect of neuregulin-1 on the mitochondrial function of cardiomyocytes. Other theories postulate that cardiac stem cells lose the ability to differentiate and form microvascular networks because of trastuzumab exposure.8

### Table 1  LVEF Monitoring and Dose Adjustments for Each HER2 Antagonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>LVEF monitoring</th>
<th>Dose adjustment</th>
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</thead>
</table>
| Trastuzumab12         | • During treatment:  
                           – Baseline and every 3 months  
                           • Posttreatment (adjuvant setting):  
                           – Every 6 months for 2 years  
                           • If treatment is withheld for LVEF dysfunction:  
                           – Every 4 weeks  
|                       | • LVEF ≥16% decrease from baseline, or below normal limits, and ≥10% decrease from baseline:  
                           – Withhold treatment for ≥4 weeks; treatment may be resumed if LVEF returns to normal within 4-8 weeks and remains at a ≤15% decrease from baseline  
                           • LVEF decrease >8 weeks, or >3 incidents of treatment interruption for cardiomyopathy: discontinue permanently |
| Ado-trastuzumab emtansine4 | • During treatment:  
                           – Baseline and every 3 months  
                           • LVEF <40% or 40%-45% with ≥10% absolute decrease below baseline:  
                           – Every 3 weeks  
|                       | • LVEF 40%-45% and ≥10% decrease from baseline:  
                           – Withhold treatment and repeat LVEF assessment within 3 weeks; if LVEF is not recovered to ≤10% from baseline, permanently discontinue  
                           • LVEF <40%:  
                           – Withhold treatment and repeat LVEF assessment within 3 weeks; if repeat LVEF <40% occurs, permanently discontinue  
                           • Symptomatic congestive heart failure:  
                           – Permanently discontinue |
| Pertuzumab5           | • Metastatic treatment:  
                           – Baseline and every 3 months  
                           • Neoadjuvant treatment:  
                           – Baseline and every 6 weeks  
                           • Posttreatment:  
                           – Every 6 months for ≤2 years from last dose of pertuzumab and/or trastuzumab  
|                       | • LVEF <45% or 45%-49% with ≥10% absolute decrease below baseline levels:  
                           – Withhold treatment with pertuzumab and trastuzumab for ≥3 weeks; treatment may be resumed if LVEF returns to >49% or 45%-49% with <10% absolute decrease below baseline levels  
                           • If LVEF has not improved within 3 weeks or has declined further:  
                           – Permanently discontinue pertuzumab and trastuzumab |
| Lapatinib6            | Baseline and periodic; if there is a risk for QT prolongation, use EKG monitoring |
|                       | • LVEF below lower limit of normal or grade ≥2 per National Cancer Institute Common Terminology Criteria for Adverse Events:  
                           – Discontinue treatment for ≥2 weeks; treatment may be resumed at a dose of 1000 mg once daily if LVEF recovers to normal and patient is asymptomatic |

EKG indicates electrocardiogram; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction.
SYMPTOM MANAGEMENT OVERVIEW

TREATMENT OPTIONS

The best management of cardiotoxicity from HER2 inhibitors is prevention. This can be accomplished by reducing known risk factors for cardiotoxicity, and through appropriate monitoring. For example, when therapy with an anthracycline and HER2 inhibitor is required, it is highly recommended that treatment with a HER2 inhibitor be given after anthracycline treatment.11 The various monitoring strategies suggested in each agent’s prescribing information are included in Table 1.4-6,12

Left ventricular ejection fractions (LVEFs) are generally checked via a multiple-gated acquisition scan or echocardiogram every 3 months during treatment with a HER2 inhibitor, with the exception of pertuzumab—in the neoadjuvant setting—and lapatinib; however, ejection fraction is not the only assessable parameter.13

Eiman Jahangir, MD, MPH, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, LA, and colleagues suggest monitoring troponin, brain natriuretic peptide (BNP), and left ventricular global longitudinal strain imaging.13 In addition, in a study led by Daniela Cardinale, MD, Cardiology Unit, Istituto Europeo di Oncologia, University of Milan, Italy, patients with elevated troponin levels were more likely to develop cardiomyopathy than patients without.14 Therefore, monitoring troponin levels may be beneficial. The utility of monitoring BNP, however, is less clear, because the data are conflicting.13

Finally, measurement of left ventricular longitudinal strain may be beneficial in predicting left ventricular dysfunction later in treatment; a strain of absolute value

Table 2 Heart Failure Treatment Agents, Doses, and Side Effects, Based on the ACCF/AHA Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
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<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
<td>Fluid retention; fatigue; bradycardia; heart block; hypotension</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>50 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Carvedilol phosphate extended release</td>
<td>10 mg once daily</td>
<td>80 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate extended release</td>
<td>12.5-25 mg once daily</td>
<td>200 mg once daily</td>
<td></td>
</tr>
<tr>
<td><strong>ACEIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50 mg three times daily</td>
<td>Rash; taste disturbances; dry cough; hypotension; renal dysfunction; hyperkalemia</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10-20 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5-10 mg once daily</td>
<td>40 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg once daily</td>
<td>20-40 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once daily</td>
<td>8-16 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice daily</td>
<td>20 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg once daily</td>
<td>10 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once daily</td>
<td>4 mg once daily</td>
<td></td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-8 mg once daily</td>
<td>32 mg once daily</td>
<td>Hypotension; renal dysfunction; hyperkalemia</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg once daily</td>
<td>50-150 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>20-40 mg twice daily</td>
<td>160 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Doses should be titrated at 1- to 2-week intervals. The goal is to keep blood pressure in a normal range; it is suggested to reach this goal within 4 weeks.15 ACCF/AHA indicates American College of Cardiology Foundation/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

below –20%, or decrease in absolute value by 10%, can signify early myocardial dysfunction and potentially predict cardiotoxicity with later treatment cycles.

Patients who develop a decreased ejection fraction generally require physicians to withhold HER2 inhibitor therapy, and monitor them more frequently (Table 1).4-6,12 Because cardiotoxicity associated with HER2 inhibitors is often reversible, withholding the HER2 inhibitor therapy, and monitor them more frequently (Table 1).4-6,12 Because cardiotoxicity associated with HER2 inhibitors is often reversible, withholding the HER2 inhibitor therapy is generally held, and a heart failure regimen started. Because cardiotoxicity associated with HER2 inhibitor therapy is generally reversible, LVEF typically returns to normal, and patients may potentially be restarted on HER2 inhibitor therapy per guidance from the drug’s package insert.4-6,12

Although the mechanism of cardiotoxicity is not well-understood, treatment strategies (eg, LVEF monitoring) can detect early signs of cardiotoxicity.

for a time and initiating therapy for heart failure may be enough to correct the decrease in ejection fraction.13 Typically, cardiotoxicity resolves over a period of 1 to 3 months following discontinuation of HER2 inhibitors.12 In addition, once a patient has a decreased ejection fraction, monitoring of troponin and BNP is more strongly encouraged.13 Because these patients have a decreased ejection fraction, they should be treated with therapy appropriate for heart failure, including treatment with beta blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (Table 2).13,16

Although these agents should be continued throughout treatment, the duration of treatment with these agents is unclear.13 Doses should be titrated at 1- to 2-week intervals, with the goal of maintaining normal blood pressure.13,16 Use of diuretics may also be necessary, as is indicated by the 2013 American College of Cardiology Foundation/American Heart Association heart failure management guidelines.13

Once a patient’s LVEF returns to baseline, most HER2 inhibitors may be resumed, especially if the HER2 inhibitor is being used with curative intent; agent-specific guidelines are available in Table 1.4-6,12 LVEF monitoring should continue after therapy completion, usually for another 2 years, at less frequent intervals.13 As was stated previously, the duration of therapy with cardioprotective agents—if started—remains unclear; however, indefinite treatment may be considered.13

**SUMMARY**

In certain settings, HER2 inhibitors are used with curative intent.15 Cardiotoxicity is a serious adverse effect that can develop in patients receiving HER2 inhibitors, and may cause dose delays for these patients.2 Therefore, recognition and treatment of cardiotoxicity is essential to maintaining dose intensity and preventing complications. Although the mechanism of cardiotoxicity is not well-understood, treatment strategies (eg, LVEF monitoring) can detect early signs of cardiotoxicity.13,14 Once cardiotoxicity develops, HER2 inhibitor therapy is generally held, and a heart failure regimen started. Because cardiotoxicity associated with HER2 inhibitor therapy is usually reversible, LVEF typically returns to normal, and patients may potentially be restarted on HER2 inhibitor therapy per guidance from the drug’s package insert.4-6,12

**References**